REMARKS

The Claim Amendments

Claims 1, 48, and 50 have been amended by deleting the alternative embodiment of Q^1 being -CONR- and the alternative embodiment of Q^2 being -NR'-. Support for these amendments is found in the claims as originally filed and in the corresponding specification text. In addition, claim 1 has been amended to improve its form by deleting periods and redundant punctuation within the body of the claim.

Claims 1, 48, and 50 have been amended such that the valency of substituents containing a phosphorus atom are clarified by using parentheses around the groups or atoms bonded to the phosphorus.

Claim 48 has been amended to recite a method of inhibiting kinase activity in a biological sample with a compound of the invention. Support for this amendment is found in paragraph [00154] on page 106 of the specification.

Claims 50, 52, and 53 have been amended to further define the diseases or disorders treated or ameliorated by the compounds of the invention. Support for these amendments can be found in paragraphs [00117] and [00135] to [00144] on pages 93 and 100 to 103, respectively.

New claims 54 to 56 recite specific diseases or diseases or disorders treated or ameliorated by the compounds of the invention. Support for these amendments can be found in paragraphs [00142] to [00144] on pages 102 to 103.

None of these amendments adds new matter. Their entry is requested

The Response

Restriction Requirement

The Examiner has recognized applicants' election of restriction Group V, drawn to compounds of formula I wherein Z^1, Z^2, and Z^3 are CR^z, corresponding compositions, and methods of use. Applicants point out that, according to the definitions provided in original claims 1, 48, and 50, this restriction group is more properly drawn to compounds of formula I wherein Z^1 and Z^3 are CR^z, and Z^2 is CR^1.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 1 and its dependent claims under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner states that the recitation of U and V as -PO- and -POR- makes the valency of these linkers unclear. Applicants argue that one skilled in the art would recognize that, in order for valency to be fulfilled in these linkers, the phosphorus atom would have to form a double bond with the oxygen atom in the first case and a single bond with the oxygen atom in the second case. To further clarify these bonding relationships, claims 1, 48, and 50 have been amended by putting parentheses around the groups bound to phosphorus [e.g., -P(O)- or -P(OR)-] to indicate the oxidation state of the base atom.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 47-53 under 35 U.S.C. § 112, second paragraph. The Examiner alleges that applicants have not provided sufficient evidence that establishes that the disclosure was enabling for one skilled in the art at the time of filing for the entire scope of the methods of use recited in the instant claims. The Examiner asserts that (i) receptor tyrosine kinase inhibition effects are unpredictable and still exploratory and that applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds; (ii) the specification has no working examples that show how to treat all of the recited diseases or disorders; (iii) the instant claims embrace treating diseases or disorders that have not yet been related to kinase inhibition; and (iv) the quantity of experimentation needed to practice the invention places an undue burden on one skilled in the pharmaceutical arts. Applicants traverse.

Amended claims 50 and 52-23, original claim 51, and new claims 54-56 recite specific diseases or disorders that may be treated by compositions of the invention, including various proliferative, cardiovascular, and neurological diseases or disorders, as well as allergies, asthma, and diabetes.

In particular, amended claim 50, *inter alia*, and amended claim 52 recite a method of treating various cancers with a compound of the invention. At the time of the invention, it was known that MAP/ERK kinases play a pivotal role in mitogenic signal transduction and that aberrant activation of signal transducing molecules, such as Ras and Raf-1, via these kinases has been linked with cancer. Hoshino et al. (see the abstract in *Oncogene* 18:813-22, 1999; hereafter "Hoshino") showed that constitutive activation of MAP/ERK kinases was found in primary tumor cell lines derived from human pancreas, colon, lung, ovary and kidney. In another study, Frey et al. (see page 47, left column, in *Cancer Lett.* 117(1):41-50, 1997; hereafter "Frey") demonstrated the ability of transforming growth factor beta-2 to potently activate ERK2 in a human tumor cell line for breast cancer. In another study, Putz et al. (see page 231, right column, in *Cancer Res.* 59(1):227-33, 1999; hereafter "Putz") demonstrated that blockade of the up-regulated ERK pathway by a monoclonal antibody antagonist abrogates IGF-1-induced p42/ERK2 activation in a human tumor cell line for prostate cancer. In yet another study, Kortylewski et al. (see page 302, right column, in *Biochem. J.* 357(Pt 1):297-303, 2001; hereafter "Kortylewski") showed that ERK is constitutively active in human tumor cell lines for melanoma. Taken together with the specification, Hoshino, Frey, Putz, and Kortylewski clearly show that there is a reasonable correlation between the inhibitors of the invention, the data showing their inhibitory activity presented in Example 2 ([00288] on page 151), and the use of these compounds to treat various cancers, as recited in amended claims 50 and 52.

Amended claim 50, *inter alia*, and amended claim 53 recite a method of treating various cardiovascular diseases with a compound of the invention. At the time of the invention, it was known that ROCK played an important role in the pathophysiology and progression of various cardiovascular diseases. Relevant art has been reviewed by Hirooka et al. in *Am. J. Cardiovasc. Drugs* 5(1):31-39, 2005 (hereafter "Hirooka"). See the discussion in section 2.1 of the use of ROCK inhibitors to induce a hypotensive effect, the discussion in sections 2.2.1 and 2.2.2 of the role of

a ROCK inhibitor in treating angina pectoris, the discussion in section 2.2.3 of the use of a ROCK inhibitor in a restenosis model, the discussion in section 2.2.4 of use of a ROCK inhibitor in a model of cardiac allograft vasculopathy, and the discussion in section 2.4 of the potential for a ROCK inhibitor to be used for the treatment of erectile dysfunction. Taken together with the specification, Hirooka shows that there is a reasonable correlation between the inhibitors of the invention, the data showing their ROCK inhibitory activity presented in Example 1 ([00285] on page 151), and the use of these compounds to treat various cardiovascular diseases, as recited in amended claims 50 and 53.

Amended claim 50, *inter alia*, and amended claim 54 recite a method of treating various neurodegenerative disorders with a compound of the invention. At the time of the invention, it was known that abnormal activation of the Rho/ROCK pathway has been observed in various disorders of the central nervous system and that ROCK inhibitors have potential for preventing neurodegeneration and stimulating neuroregeneration in various neurological disorders. Relevant art has been reviewed by Mueller et al., *Nature Reviews* 4:387-398, 2005 (hereafter "Mueller"). See the right hand column of page 391 of Mueller for a discussion of the effect of ROCK inhibition on enhancing nerved growth and in neuroprotection. Also discussed on paged 391 to 392 of Mueller is the lowering of Aβ42 levels by a ROCK inhibitor for the treatment of Alzheimer's disease. In addition, it was also known at the time of the invention that GSK-3 was a potential therapeutic target for treating Alzheimer's disease. See the abstract and Table 2 on page 1182 of Doble et al., *J. Cell Sci.* 116:1175-1186, 2003 (hereafter "Doble"). Taken together with the specification, Mueller and Doble show that there is a reasonable correlation between the inhibitors of the invention, the data showing their ROCK or GSK-3 inhibitory activity presented in Examples 1 and 3 ([00285] on page 151 and [00292] on page 152, respectively), and the use of these compounds to treat various neurological disorders, as recited in amended claims 50 and 54.

Amended claim 50, *inter alia*, and amended claim 55 recite a method of

treating an allergy or asthma with a compound of the invention. The role of ERK in treating allergy and asthma was established at the time of the invention. For example, it was known at the time of the invention that the survival and apoptosis of eosinophils is of pivotal importance for controlling allergic diseases, such as asthma. Chang et al. (see page 36 of *Cell Immunol.* 203(1):29-38, 2000; hereafter "Chang") showed that an MAP/ERK kinase inhibitor was partly able to block augmentation of eosinophil viability in cell culture studies. Taken together with the specification, Chang clearly shows that there is a reasonable correlation between the inhibitors of the invention, the data showing their inhibitory activity, and the use of these compounds to treat allergy/asthma, as recited in amended claims 50 and 55.

Amended claim 50, *inter alia*, and amended claim 56 recite a method of treating diabetes with a compound of the invention. At the time of the invention, it was known that inhibition of GSK-3 could be useful in the treatment of diabetes. Plotkin et al., (see abstract of *J. Pharm. Exp. Ther.* 305(3):974-980, 2003; hereafter "Plotkin") showed that a GSK-3 inhibitor could activate glycogen synthase activity 2.5-foled in human embryonic kidney cells and increase glucose uptake in primary mouse adipocytes. Taken together with the specification, Plotkin clearly shows that there is a reasonable correlation between the inhibitors of the invention, the data showing their GSK-3 in Example 3 ([00292] on page 152) inhibitory activity, and the use of these compounds to treat diabetes, as recited in amended claims 50 and 56.

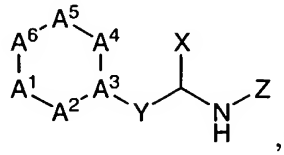
Regarding the Examiner's objection that the specification allegedly fails to guide or enable the skilled artisan to practice the invention without undue experimentation, the term "undue experimentation" applies to that requiring ingenuity beyond that expected of one of ordinary skill in the art. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine" (MPEP 2164.06). In each case, the indicated treatment is enabled in the specification and methods of administering the compounds of the invention are taught (see [00124] to [00134] on pages 96-100). A skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided

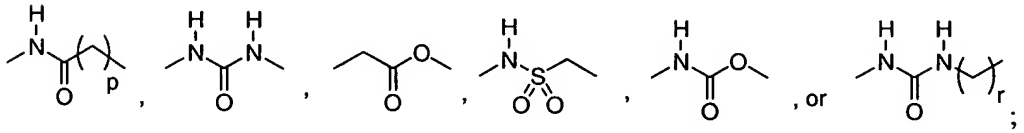
in the specification along with the general knowledge of one skilled in the art. Thus, the claimed invention is enabled by the specification as originally filed.

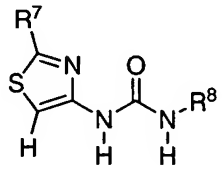
Rejection under 35 U.S.C. § 103(a)

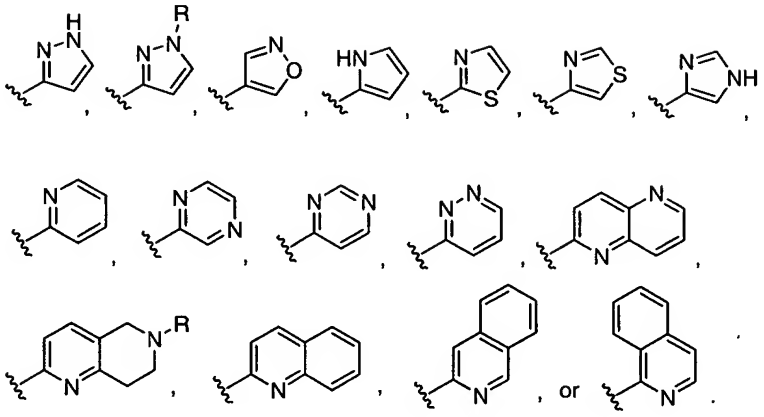
The Examiner has rejected claims 1-47 and 50-53 under 35 U.S.C. § 103(a) as allegedly being obvious over Santora et al., PCT Publication No. WO 02/14311 (hereafter, "the '311 application") [Note, in the November 21st Office Action, a typographical error was made, with the Examiner citing this reference as US2004/0220177. In a subsequent telephone conversation, the Examiner identified this reference as the '311 application.].

The Examiner asserts that the compounds taught in Examples 1-233 of the '311 application are equivalent to those compounds that are generically recited having the formula:


, where Y is

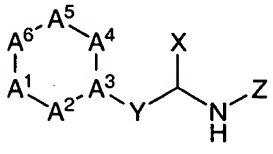

; and further points to compounds in the '311 application having the formula:


, where R^8 is selected from

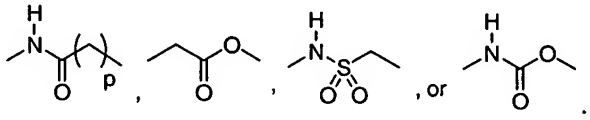


The Examiner then alleges that it would have been obvious to one having ordinary skill in the art to make the compounds of the instant invention and expect those compounds to possess the uses taught by the art in view of the "equivalency" of Examples 1-233 to the generic formulae of the '311 application. Applicants traverse.

The '311 application discloses a genus and various subgenera covering a vast number of compounds. However, the '311 application only exemplifies compounds with a urea linkage representing Y in the formula above, where R is hydrogen or a methyl group. Therefore, contrary to the Examiner's assertion, the '311 application does not demonstrate equivalency of the urea compounds exemplified in the '311 application to any of the vast number of generically-described compounds of the '311 application that have the formula:



, wherein Y is



In contrast, the instant claims do not recite compounds that have a urea linkage and the '311 application does not teach or suggest the genus recited in the claims. In addition, the '311 application only teaches the use of the compounds of Examples 1-35 for the inhibition of CDK2 and CDK5, the use of the compound of Example 36 for the inhibition of KDR, and the activity of the compounds of Examples 14 and 43 in an ischemic stroke model (see, for example, pages 295-301 of the '311 application). The

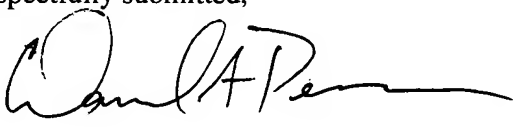
'311 application does not teach or suggest modifying the compounds taught in the specification to inhibit ROCK, ERK, GSK-3 or AGC, as taught in the specification.

As the '311 application does not teach or suggest compounds useful for inhibiting the kinases inhibited by the compounds of the instant invention and since the Examiner has recognized that the instant claims exclude the specific compounds taught in the '311 application, the compounds of the '311 application do not teach or suggest the compounds or methods recited by the instant claims. Applicants therefore respectfully request that the Examiner withdraw his rejection of the instant claims under 35 U.S.C. § 103(a).

Conclusion

Applicants request that the Examiner enter the above amendments, consider the accompanying arguments, and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the Examiner contact the undersigned at his convenience.

Respectfully submitted,



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